27 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 6, 13, 17, and 25 are amended. Support for the amendment is found in the original specification; no new matter was added in this amendment. Applicants respectfully request that the Examiner withdraw the rejection.

Double Patenting

Examiner has rejected Claims 10-11 under the judicially created doctrine of obviousness-type double patenting. as being unpatentable over Claims 1-2 of copending Application No 09/425,633. However, claims 1-2 of said copending Application have been canceled in an amendment dated February 26, 2001. Only Claims 17-41 are pending in the 09/425,633 case. Since Claims 1-2 of 09/425,633 are no longer pending, the issue of double patenting is moot. As such, Applicants respectfully request the Examiner to withdraw this rejection.

Priority

Examiner claims that there is a discrepancy in the number of applications claimed as priority applications. In particular, the first paragraph of the specification does not list application No. 09/425,633, which was listed in the Declaration and in the Second Request for Corrected Official Filing Receipt. In response, Applicants note that the "first paragraph of the specification, amended October 30, 2000," has been amended listing Application No. 09/425,633 and complies with 37 CFR 1.78. Support for this amendment can be found in the original specification and the executed Inventor Declaration submittal; no new matter was added in this amendment. A "Marked-Up Version" of the amended specification is attached. Additionally, a copy of the "Preliminary Amendment" mailed October 24, 2000 is attached for the Examiner's convenience. Applicants would like to point out to the Examiner that the

Application No. 09/425,633 was referenced in said preliminary amendment.

Claim Rejections under 35 U.S.C.§112

Here, Examiner rejected Claims 1-17 and 22-27 under 35 U.S.C: 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. First, Applicants would like to thank Examiner for her interview on October 19, 2001. As discussed in the interview, Applicants and Examiner agree that one microsphere can be randomly distributed. In addition, Claims have been amended to recite with more particularity that which the Applicants consider as the invention. In particular language has been added to vitiate rejections based on insufficient antecedent basis, and entry thereof into the instant application is respectfully requested.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and an early notification of such is solicited. If, upon review, the Examiner feels there are additional outstanding issues, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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Date: 11/8/01

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MARKED-UP VERSION

In the Specification

This application is a [continuation-in-part] continuing application of 09/324,633, filed October 22, 1999 and claims the benefit of priority of U.S.S.N.s 60/130,089 filed April 20, 1999; 60/135,051, filed May 20, 1999; 60/135,053, filed May 20, 1999; 60/135,123, filed May 20, 1999; [and 09/324,633, filed on October 22, 1999;] and 60/160,917, filed October 22, 1999.

In the Claims

1. A method of sequencing a plurality of target nucleic acids each comprising a first domain and an adjacent second domain, said second domain comprising a plurality of target positions, said method comprising:

a) providing first and second hybridization complexes comprising first and second target sequences, respectively and first and second sequencing primers, respectively, that hybridize to the first domain of said first and second target sequences, respectively, said first and second hybridization complexes attached to first and second microspheres, respectively, randomly distributed on a surface of a substrate;

b) extending said first and second primers by the addition of a first nucleotide to [the] a first detection position using a first enzyme to form first and second extended primer, respectively; and

c) detecting the release of pyrophosphate (PPi) to determine the type of said first nucleotide added onto said first and second primers, respectively.

6. (Amended) A method according to claim 1 further comprising:

(d) extending said first and second extended primers by the addition of [the] a

second nucleotide to a second detection position using said first enzyme; and

(e) detecting the release of pyrophosphate (PPi) to determine the type of said second nucleotide added onto said first and second primers, respectively.

13. (Amended) A method according to claim 10 wherein said determining comprises:

a) providing a sequencing primer hybridized to said second domain;

b) extending said primer by the addition of [the] a first nucleotide to a first detection position using a first enzyme to form an extended primer;

c) detecting the release of pyrophosphate (PPi) to determine the type of said first nucleotide added onto said primer;

d) extending said primer by the addition of a second nucleotide to [the] a second detection position using said enzyme; and

e) detecting the release of pyrophosphate (PPi) to determine the type of said first nucleotide added onto said primer.

17. (Amended) A method according to claim 10 wherein said determining comprises:

a) providing a sequence primer hybridized to said second domain;

b) extending said primer by the addition of a first protected nucleotide using a first enzyme to form an extended primer;

c) determining the identification of said first protected nucleotide;

d) removing the protection group;

e) adding a second protected nucleotide using said first enzyme; and

f) determining the identification of said second protected nucleotide.

25. (Amended) The method according to claim 10, wherein [said] discrete sites are wells, and said microspheres are randomly distributed in said wells.

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PENDING CLAIMS

1. A method of sequencing a plurality of target nucleic acids each comprising a first domain and an adjacent second domain, said second domain comprising a plurality of target positions, said method comprising:

a) providing first and second hybridization complexes comprising first and second target sequences, respectively and first and second sequencing primers, respectively, that hybridize to the first domain of said first and second target sequences, respectively, said first and second hybridization complexes attached to first and second microspheres, respectively, randomly distributed on a surface of a substrate;

b) extending said first and second primers by the addition of a first nucleotide to a first detection position using a first enzyme to form first and second extended primer, respectively; and

c) detecting the release of pyrophosphate (PPi) to determine the type of said first nucleotide added onto said first and second primers, respectively.

2. A method according to claim 1 wherein at least said first hybridization complex is covalently attached to said first microsphere.

3. A method according to claim 1 wherein at least said first sequencing primer is attached to said first microsphere.

4. A method according to claim 1 wherein said first and second hybridization complexes comprise said first and second target sequences, respectively, said first and second sequencing primers, respectively, and first and second capture probes, respectively, covalently attached to said first and second microspheres, respectively.

5. A method according to claim 1 wherein said first and second hybridization complexes

comprise said first and second target sequences, respectively, said first and second sequencing primers, a first and second adapter probe, respectively, and first and second capture probes, respectively, covalently attached to said first and second microspheres.

6. A method according to claim 1 further comprising:

d) extending said first and second extended primers by the addition of a second nucleotide to a second detection position using said first enzyme; and

e) detecting the release of pyrophosphate (PPi) to determine the type of said second nucleotide added onto said first and second primers, respectively.

7. The method according to claim 1 wherein said PPi is detected by a method comprising:

a) contacting said PPi with a second enzyme that converts said PPi into ATP; and

b) detecting said ATP using a third enzyme.

8. A method according to claim 7 wherein said second enzyme is sulfurylase.

9. A method according to claim 7 wherein said third enzyme is luciferase.

10. A method of sequencing a target nucleic acid comprising a first domain and an adjacent second domain, said second domain comprising a plurality of target positions, said method comprising:

a) providing a hybridization complex comprising said target sequence and a capture probe covalently attached to a microsphere randomly distributed on a surface of a substrate; and

b) determining the identity of a plurality of bases at said target positions.

11. A method according to claim 10 wherein said hybridization complex comprises said

capture probe, an adapter probe, and said target sequence.

12. A method according to claim 10 wherein said capture probe is a sequencing primer.

13. A method according to claim 10 wherein said determining comprises:

a) providing a sequencing primer hybridized to said second domain;

b) extending said primer by the addition of a first nucleotide to a first detection position using a first enzyme to form an extended primer;

c) detecting the release of pyrophosphate (PPi) to determine the type of said first nucleotide added onto said primer;

d) extending said primer by the addition of a second nucleotide to a second detection position using said enzyme; and

e) detecting the release of pyrophosphate (PPi) to determine the type of said first nucleotide added onto said primer.

14. The method according to claim 13 wherein said PPi is detected by a method comprising:

a) contacting said PPi with a second enzyme that converts said PPi into ATP; and

b) detecting said ATP using a third enzyme.

15. A method according to claim 14 wherein said second enzyme is sulfurylase.

16. A method according to claim 14 wherein said third enzyme is luciferase.

17. A method according to claim 10 wherein said determining comprises:

a) providing a sequence primer hybridized to said second domain;

b) extending said primer by the addition of a first protected nucleotide using a first enzyme to form an extended primer;

c) determining the identification of said first protected nucleotide;

d) removing the protection group;

e) adding a second protected nucleotide using said first enzyme; and

f) determining the identification of said second protected nucleotide.

18. A kit for nucleic acid sequencing comprising:

a) a composition comprising:

i) a substrate with a surface comprising discrete sites; and

ii) a population of microspheres randomly distributed on said sites;

wherein said microspheres comprise capture probes;

b) an extension enzyme; and

c) dNTPs.

19. A kit according to claim 18 further comprising:

d) a second enzyme for the conversion of pyrophosphate (PPi) to ATP; and

e) a third enzyme for the detection of ATP.

20. A kit according to claim 18 wherein said dNTPs are labeled.

21. A kit according to claim 20 wherein each dNTP comprises a different label.

22. The method according to claim 1, wherein said substrate comprises discrete sites and said first and second microspheres are randomly distributed on said sites.

23. The method according to claim 22, wherein said discrete sites are wells, and said first and second microspheres are randomly distributed in said wells.

24. The method according to claim 10, wherein said substrate comprises discrete sites and

said microspheres are randomly distributed on said sites.

25. The method according to claim 10, wherein discrete sites are wells, and said microspheres are randomly distributed in said wells.

26. The method according to claim 1, 10, 22, 23, 24 or 25, wherein said substrate is a fiber optic bundle.

27. The method according to claim 1, 10, 22, 23, 24 or 25, wherein said substrate is selected from the group consisting of glass and plastic.

28. The kit according to claim 18, wherein discrete sites are wells.

29. The kit according to claim 18 or 28, wherein said substrate is a fiber optic bundle.

30. The kit according to claim 18 or 28, wherein said substrate is selected from the group consisting of glass and plastic.